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Original article

Defining a positive circumferential resection margin in oesophageal cancer and its implications for adjuvant treatment

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Background: **A positive circumferential resection margin (CRM) has been associated with a poorer prognosis in oesophageal and oesophagogastric junctional (OGJ) cancer. The College of American Pathologists defines the CRM as positive if tumour cells are present at the margin, whereas the Royal College of Pathologists also include tumour cells within 1 mm of this margin. The relevance of these differences is not clear and no study has investigated the impact of adjuvant therapy. The aim was to identify the optimal definition of an involved CRM in patients undergoing resection for oesophageal or OGJ cancer, and to determine whether adjuvant radiotherapy improved survival in patients with an involved CRM.**

Methods: **This was a single-centre retrospective study of patients who had undergone attempted curative resection for a pathological T3 oesophageal or OGJ cancer. Clinicopathological variables and distance from the tumour to the CRM, measured to ± 0.1 mm, were correlated with survival.**

Results: **A total of 226 patients were included. Sex ($P = 0{\cdot}018$), tumour differentiation ($P = 0{\cdot}019$), lymph node status ($P < 0{\cdot}001$), number of positive nodes ($P < 0{\cdot}001$), and CRM distance ($P = 0{\cdot}042$) were independently predictive of prognosis. No significant survival difference was observed between positive CRM 0-mm and 0·1–0·9-mm groups after controlling for other prognostic variables. Both groups had poorer survival than matched patients with a CRM at least 1 mm clear of tumour cells. Among patients with a positive CRM of less than 1 mm, those undergoing observation alone had a median survival of 18·6 months, whereas survival was a median of 10 months longer in patients undergoing adjuvant radiotherapy, but otherwise matched for prognostic variables ($P = 0{\cdot}009$).**

Conclusion: **A positive CRM of 1 mm or less should be regarded as involved. Adjuvant radiotherapy confers a significant survival benefit in selected patients with an involved CRM.**

Presented in part to a meeting of the Digestive Disorders Federation, Liverpool, UK, June 2012; published in abstract form as *Gut* 2012; **61**(Suppl 2): A260

Paper accepted 7 March 2013
Published online 24 April 2013 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9145

Introduction

Oesophageal cancer is the sixth leading cause of cancer death worldwide and surgical resection remains the cornerstone of attempted curative therapy[1]. Microscopic identification of residual tumour at the proximal or distal resection margin (termed R1) increases the risk of recurrence and disease-related mortality[2]. Patients are therefore most likely to benefit from surgery if a microscopically complete (R0) resection is achieved.

The importance of microscopic disease at the circumferential resection margin (CRM) was first reported in 1993; a higher risk of local recurrence was observed when tumour deposits were present at the radial margin of oesophageal resection specimens[3]. Parallels have been drawn between rectal and oesophageal cancer as both can extend radially into surrounding tissues. In rectal cancer, identification of tumour cells at or within 1 mm of the CRM increases the risk of local recurrence and disease-related mortality[4–6].

The Royal College of Pathologists (RCP) has defined an involved CRM for oesophageal cancer as the presence of tumour cells within 1 mm of the radial resection margin, in keeping with the rectal cancer classification[7]. In contrast,

the College of American Pathologists (CAP) considers the CRM as involved if tumour cells are observed at the margin[8]. Several studies have found a poorer prognosis for patients with an involved CRM, although the definition used has varied[9–16]. In some of these studies, however, tumour differentiation[9,16] and number of involved lymph nodes[9,10,12] were not considered in multivariable analyses, potentially limiting the conclusions drawn. Two papers reported a prognostic impact when patients were stratified by distance from the tumour to the CRM[15,16]. One study reported no survival difference between groups with a positive CRM of 0 mm *versus* 0·1–0·9 mm[15]. The other, involving patients undergoing neoadjuvant chemoradiotherapy followed by surgery, identified a poorer prognosis only for patients with a CRM of 0 mm[16].

A positive CRM must reflect the extent of wall invasion (tumour category, T) and there is a clear link between increasing T category and the likelihood of lymph node involvement. The central importance of lymph node metastases in determining the prognosis of patients with oesophageal or oesophagogastric junctional (OGJ) cancer is widely accepted[17,18]. To reflect this, the seventh edition of the tumour node metastasis (TNM) staging system stratifies node status, with node-positive disease classified as N1 for one or two, N2 denoting three to six and N3 denoting seven or more positive nodes[19]. The effect of distance of the tumour to the CRM on survival can therefore be assessed only when confounding prognostic variables such as lymph node metastasis have been taken into account.

A unified definition of the involved CRM would allow straightforward comparison between trials. In turn this might lead to some clarity regarding the use of adjuvant therapies, in the absence of good evidence at present. The aims of this study were therefore: to establish whether an involved CRM was associated with poorer prognosis and to determine which classification provided the most useful prognostic information in patients undergoing neoadjuvant chemotherapy followed by surgery, or surgery alone for oesophageal or OGJ cancer; and to examine the influence of adjuvant radiotherapy on survival in selected patients with an involved CRM.

Methods

De-identified treatment and outcome data for patients undergoing attempted curative resection of oesophageal or OGJ cancer between 1994 and 2010 at the Royal Infirmary of Edinburgh were obtained from a prospectively maintained surgical audit database. Only clinical data obtained as part of routine treatment were used for this study. No additional patient consent was needed and ethical approval was not required.

Patients with a pathological (p)T3, as defined in the seventh edition of the TNM staging manual[19], adenocarcinoma or squamous cell carcinoma of the mid or distal oesophagus or oesophagogastric junction (Siewert type I–III) were included. Patients with macroscopic residual disease at surgery (R2 resection), tumour within 1 mm of the proximal or distal resection margins, or unavailability of original pathology specimens for review, and those who died within 30 days of surgery were excluded. Demographic, surgical and oncological treatment, pathological and survival data were available for all remaining patients. Survival was defined as time from diagnosis to death from any cause or last follow-up with primary or tertiary care, censoring in January 2012.

All patients were staged using a combination of computed tomography (CT), CT–positron emission tomography and endoscopic ultrasonography, and selected for surgical treatment by a multidisciplinary team comprising surgeons, gastroenterologists, oncologists, radiologists and pathologists. All resections consisted of *en bloc* oesophageal dissection with mediastinal and upper abdominal lymphadenectomy, with the approach tailored to the tumour location and patient physiology. From 2001 onwards, neoadjuvant chemotherapy was offered routinely to patients without contraindicating co-morbidity and with clinical T3 disease and/or nodal metastasis identified on preoperative staging. This consisted of either two cycles of cisplatin and 5-fluorouracil, or three or four cycles of epirubicin, cisplatin and capecitabine. Neoadjuvant radiotherapy was not used.

The oesophageal CRM was inked by the reporting pathologist before dissection. Fixed specimens were then sliced into 5-mm transverse segments, and representative blocks incorporating the closest proximity of the tumour to the inked margin were embedded for histological review. The shortest distance from the tumour to the CRM was recorded to ±0·1 mm. As UK standards of pathology reporting changed during the study period, all specimens were re-reported for this analysis by a single expert pathologist using the criteria in the seventh edition of the TNM staging manual[19]. Tumour differentiation was described by the most poorly differentiated area in the resection specimen.

The pathological findings for each resection were discussed at a multidisciplinary meeting. Selected patients with a positive CRM closer than 1 mm were offered adjuvant radiotherapy comprising 50 Gy delivered in 20 daily fractions over 4 weeks using a three- or four-field technique. The target radiotherapy volume was planned using a combination of preoperative CT, endoscopic ultrasonography, operative and pathological findings. The

field was designed to encompass the preoperative site of the tumour with a minimum radial, superior and inferior margin of 2 cm. Radiotherapy was generally commenced 8 weeks after surgery, postoperative recovery permitting.

Statistical analysis

Continuous variables are summarized as median (range) or mean (95 per cent confidence interval) as appropriate. Categorical variables were compared using the χ^2 test.

To determine the effect of demographic and pathological variables on survival, univariable analysis was performed using the Kaplan–Meier method with a log rank test of significance for categorical co-variables and Cox regression for continuous co-variables[20,21]. Co-variables found to be significantly associated with survival on univariable analysis ($P < 0{\cdot}050$) were assessed in a Cox proportional hazards model[22]. Owing to the bias in established prognostic variables across groups stratified by CRM distance, the method of propensity score matching analysis (PSMA) was applied[23]. This method has the advantage over Cox regression of generating two groups matched for confounders and differing by the treatment of interest so the magnitude of treatment effect can be estimated. This technique has been reviewed thoroughly elsewhere[24] but, briefly, PSMA uses binary logistic regression to incorporate and balance all known confounders by their ability to predict the presence or absence of the investigated variable. With known co-variables the probability of the presence of the investigated variable can be derived, termed the propensity score. Propensity scores are calculated for all patients and then each case in the treated group is paired with a control in the untreated group with a similar propensity score. A nearest neighbour with replacement strategy was used as this allows the closest approximation of scores to generate the best matched groups that differ only by the treatment investigated[25]. As the propensity score-matched groups were selected rather than independent, Cox regression stratified by quintiles of propensity score was used to evaluate the significance of survival differences[26,27]. To estimate the magnitude of survival differences between propensity score-matched groups, the Wilcoxon matched-pairs signed rank test was used, with pairs defined as informative if the shorter survivor was not censored[27]. Statistical significance was defined as $P < 0{\cdot}050$. All statistical analysis was performed using SPSS® software version 19.0.0 (IBM, Armonk, New York, USA).

Results

A total of 428 patients underwent resection during the study period. Some 202 patients were excluded for the following reasons: non-pT3 tumours (149), tumour less than 1 mm from the proximal or distal resection margin (26), postoperative death within 30 days (12), blocks unavailable for pathological review (10), histology other than adenocarcinoma or squamous cell carcinoma (3) and R2 resection (2). A summary of demographic and pathological characteristics of the remaining 226 patients is provided in *Table 1*. The median age was 64 (39–82) years. The estimated 5-year survival rate of this cohort was 25 per cent, with a median survival of 28 (4–181) months and a median follow-up of 35 months for the 70 surviving patients.

Tumours were resected via a right thoracotomy and laparotomy (Ivor Lewis oesophagectomy) in 190 patients (84·1 per cent), left thoracolaparotomy in 25 (11·1 per cent), transhiatal resection in five (2·2 per cent), extended total gastrectomy in five (2·2 per cent), and thoracoscopy and laparotomy in one patient (0·4 per cent). The median nodal harvest was 21 (3–56) nodes, with more than ten nodes examined in 92·9 per cent of patients.

Sex, tumour differentiation, lymph node status, number of positive lymph nodes and shortest distance from tumour cells to the CRM were all significantly associated with survival (*Table 1*). Patient age, tumour site, histology, operation type, year of resection and neoadjuvant chemotherapy use had no association with survival on univariable analysis. In the multivariable model, number of involved nodes ($P < 0{\cdot}001$), node status ($P < 0{\cdot}001$), tumour differentiation ($P = 0{\cdot}019$), sex ($P = 0{\cdot}018$) and CRM distance ($P = 0{\cdot}042$) remained independently predictive of survival.

Survival stratified by circumferential resection margin

When patients were grouped by distance from the closest point on the tumour to the CRM (0 mm, 0·1–0·9 mm, 1 mm or more), there was a significant association with prognosis ($P = 0{\cdot}019$ across groups) (*Table 1*, *Fig. 1a*). Patients with a close or directly involved CRM had more extensive lymphatic metastasis ($P = 0{\cdot}002$) (*Table 2*). To correct for this, propensity score-matched groups were created that were closely matched for those variables shown above to affect prognosis (*Table 2*). Propensity score-stratified univariable Cox regression analysis revealed a significantly poorer survival when the distance to the CRM was 0 mm compared with 1 mm or more ($P = 0{\cdot}033$); the hazard ratio (HR) for death was 1·70 (95 per cent confidence interval 1·04 to 2·78). There was no difference between groups with a positive CRM of 0 mm *versus* 0·1–0·9 mm ($P = 0{\cdot}549$). A significantly poorer survival was also noted for the CRM 0·1–0·9-mm group when compared independently with a propensity score-matched

Table 1 Cohort characteristics and survival analysis

	No. of patients ($n = 226$)*	Median survival (months)†	Univariable P¶	Multivariable P**
Sex			0·001	0·018
M	183 (81·0)	23·0 (18·5, 27·5)		
F	43 (19·0)	69·0 (23·3, 114·7)		
Tumour location			0·664	–
Mid oesophagus	24 (10·6)	28·0 (11·7, 44·3)		
Distal oesophagus	61 (27·0)	29·0 (18·0, 40·0)		
Type I junctional	77 (34·1)	22·0 (16·1, 27·9)		
Type II junctional	48 (21·2)	27·0 (15·1, 38·9)		
Type III junctional	16 (7·1)	50·0 (0, 136·2)		
Neoadjuvant therapy			0·189	–
Yes	130 (57·5)	29·0 (20·6, 37·4)		
No	96 (42·5)	25·0 (18·8, 31·2)		
Histology			0·051	–
ACC	184 (81·4)	25·0 (19·3, 30·7)		
SCC	42 (18·6)	44·0 (29·6, 58·4)		
Differentiation			0·002	0·019
Well	5 (2·2)	76·0 (0, 160·3)		
Moderate	92 (40·7)	34·0 (25·8, 42·2)		
Poor	129 (57·1)	21·0 (17·0, 24·9)		
Node status			< 0·001	< 0·001
N0	44 (19·5)	84·0 (36·3, 131·7)		
N1	65 (28·8)	31·0 (26·7, 35·3)		
N2	65 (28·8)	28·0 (19·3, 36·7)		
N3	52 (23·0)	14·0 (12·0, 16·0)		
CRM (mm)			0·019	0·042
0	47 (20·8)	18·0 (13·0, 23·0)		
0·1–0·9	83 (36·7)	28·0 (18·7, 37·4)		
≥ 1	96 (42·5)	33·0 (25·8, 40·2)		
Continuous variables‡				
Age (years)	64 (39–82)	1·00 (0·98, 1·02)§	0·681#	–
No. of positive lymph nodes	3 (0–23)	1·12 (1·09, 1·16)§	< 0·001#	< 0·001

Values in parentheses are *percentages and †95 per cent confidence intervals unless indicated otherwise; ‡values for continuous variables are median (range) with §hazard ratios. ACC, adenocarcinoma; SCC, squamous cell carcinoma; CRM, circumferential resection margin. ¶Log rank test, except #Cox regression; **Cox proportional hazards model.

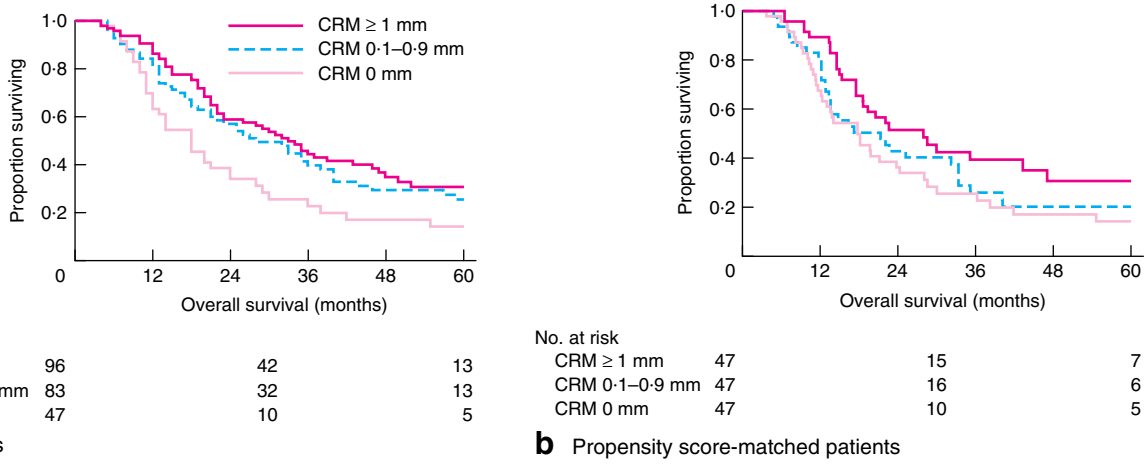

Fig. 1 Kaplan–Meier curves for **a** all patients and **b** propensity score-matched patients stratified by distance to the circumferential resection margin (CRM)

Table 2 Characteristics of circumferential resection margin groups

	Unselected patients†			Propensity score-matched to CRM 0 mm‡			Propensity score-matched to CRM 0.1–0·9 mm§	
	CRM 0 mm ($n = 47$)	CRM 0·1–0·9 mm ($n = 83$)	CRM ≥ 1 mm ($n = 96$)	CRM 0 mm ($n = 47$)	CRM 0·1–0·9 mm ($n = 47$)	CRM ≥ 1 mm ($n = 47$)	CRM 0·1–0·9 mm ($n = 83$)	CRM ≥ 1 mm ($n = 83$)
Sex								
M	40	66	77	40	40	40	66	66
F	7	17	19	7	7	7	17	17
Neoadjuvant therapy								
Yes	23	51	56	23	20	25	51	61
No	24	32	40	24	27	22	32	22
Histology								
ACC	41	63	80	41	43	42	63	60
SCC	6	20	16	6	4	5	20	23
Differentiation								
Well	2	3	0	2	2	0	3	0
Moderate	14	36	42	14	13	16	36	28
Poor	31	44	54	31	32	31	44	55
Node status								
N0	4	18	22	4	6	3	18	24
N1	11	20	34	11	9	11	20	18
N2	11	29	25	11	10	7	29	25
N3	21	16	15	21	22	26	16	16
Median survival (months)*	18·0 (13·0, 23·0)	28·0 (18·7, 37·4)	33·0 (25·8, 40·2)	18·0 (13·0, 23·0)	21·4 (11·9, 30·8)	28·0 (18·0, 38·0)	28·0 (18·7, 37·4)	47·2 (43·3, 51·1)

*Values in parentheses are 95 per cent confidence intervals. CRM, circumferential resection margin; ACC, adenocarcinoma; SCC, squamous cell carcinoma. Comparison of node status: †$P = 0·002$, ‡$P = 0·825$, §$P = 0·739$ (χ^2 test).

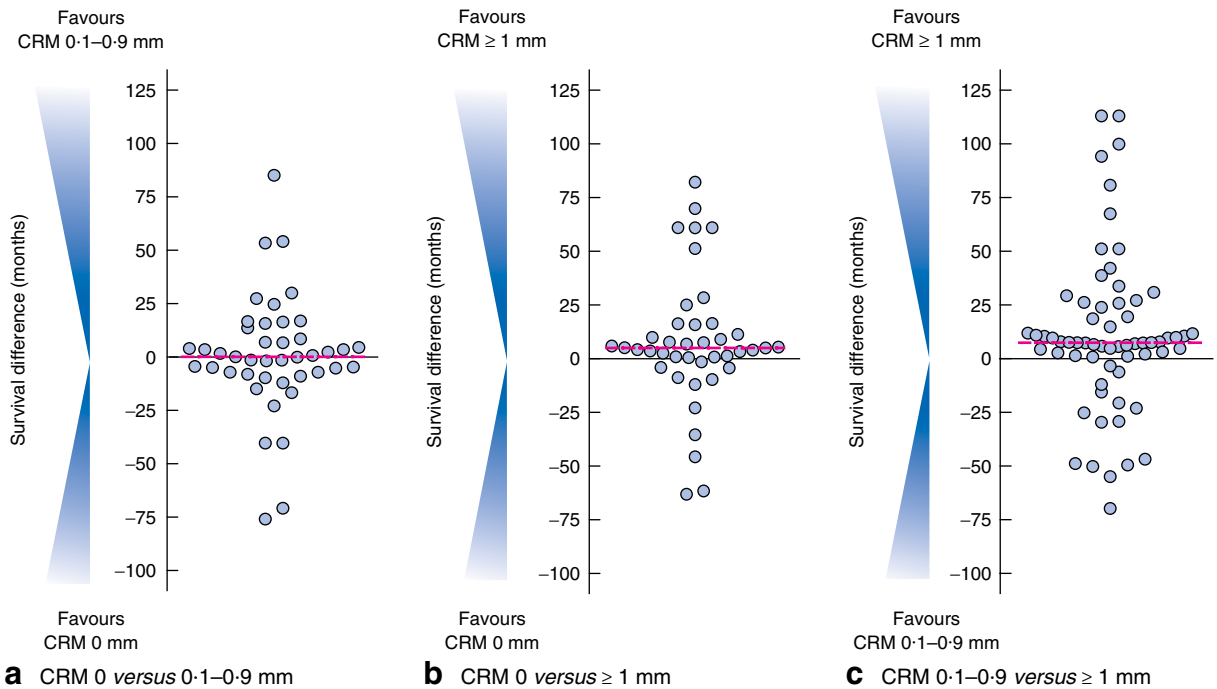

Fig. 2 Scatter plots of survival differences between propensity score-matched pairs. Survival differences from informative pairs are shown: **a** circumferential resection margin (CRM) 0 mm *versus* 0·1–0·9 mm ($n = 43$), **b** CRM 0 mm *versus* 1 mm or more ($n = 41$) and **c** CRM 0·1–0·9 mm *versus* 1 mm or more ($n = 64$). Dashed red lines represent median values. **a** $P = 0·837$, **b** $P = 0·038$, **c** $P = 0·005$ (Wilcoxon matched-pairs signed rank test)

Table 3 Comparison of unselected and propensity score-matched patients with a positive circumferential resection margin of less than 1 mm treated by adjuvant radiotherapy or observation alone

	Unselected†		Propensity score-matched‡	
	Observation (*n* = 52)	Adjuvant radiotherapy (*n* = 23)	Observation (*n* = 23)	Adjuvant radiotherapy (*n* = 23)
Sex				
M	44	17	16	17
F	8	6	7	6
Neoadjuvant therapy				
Yes	52	23	23	23
No	0	0	0	0
Histology				
ACC	48	13	14	13
SCC	4	10	9	10
Differentiation				
Well	2	1	1	1
Moderate	14	10	10	10
Poor	36	12	12	12
Node status				
N0	5	11	14	11
N1	8	9	7	9
N2	18	3	2	3
N3	21	0	0	0
CRM (mm)				
0	17	7	5	7
0·1–0·9	35	16	18	16
Adjuvant radiotherapy				
Yes	0	23	0	23
No	52	0	23	0
Median survival (months)*	17·0 (10·7, 23·3)	96·0 (14·9, 177·0)	18·6 (8·6, 28·6)	96·0 (14·9, 177·0)

*Values in parentheses are 95 per cent confidence intervals. ACC, adenocarcinoma; SCC, squamous cell carcinoma; CRM, circumferential resection margin. Comparison of node status: †$P < 0·001$, ‡$P = 0·667$ (χ^2 test).

group with a CRM of 1 mm or more ($P = 0·029$); the HR was 1·53 (1·04 to 2·27) (*Table 2*).

There was no difference in length of survival between propensity score-matched pairs selected from positive CRM 0-mm and CRM 0·1–0·9-mm groups when adverse prognostic factors such as lymph node metastasis were taken into account. Compared with propensity score-matched patients with a positive CRM of 1 mm or greater, survival was significantly poorer by a median of 5 months for patients with a CRM of 0 mm and by 7 months for those with a CRM of 0·1–0·9 mm (*Fig. 2*).

Treatment of the positive circumferential resection margin

The cohort contained 75 patients who had undergone neoadjuvant chemotherapy and had a positive CRM closer than 1 mm. Within this group, 23 patients underwent adjuvant radiotherapy. There was a significant selection bias for these patients, with a predominance of squamous cell carcinomas, and patients with N0 and N1 disease ($P < 0·001$) (*Table 3*). The remainder of the group underwent postoperative observation only and had a significantly poorer survival ($P = 0·001$) (*Fig. 3a*).

Propensity score matching was applied to create two well matched groups differing only in the use of adjuvant radiotherapy. Patients receiving adjuvant radiotherapy had a median survival of 96·0 (95 per cent confidence interval 14·9 to 177·0) months compared with 18·6 (8·6 to 28·6) months for those managed by observation alone ($P = 0·009$) (*Table 3*, *Fig. 3b*); the HR for death was 0·50 (0·30 to 0·84).

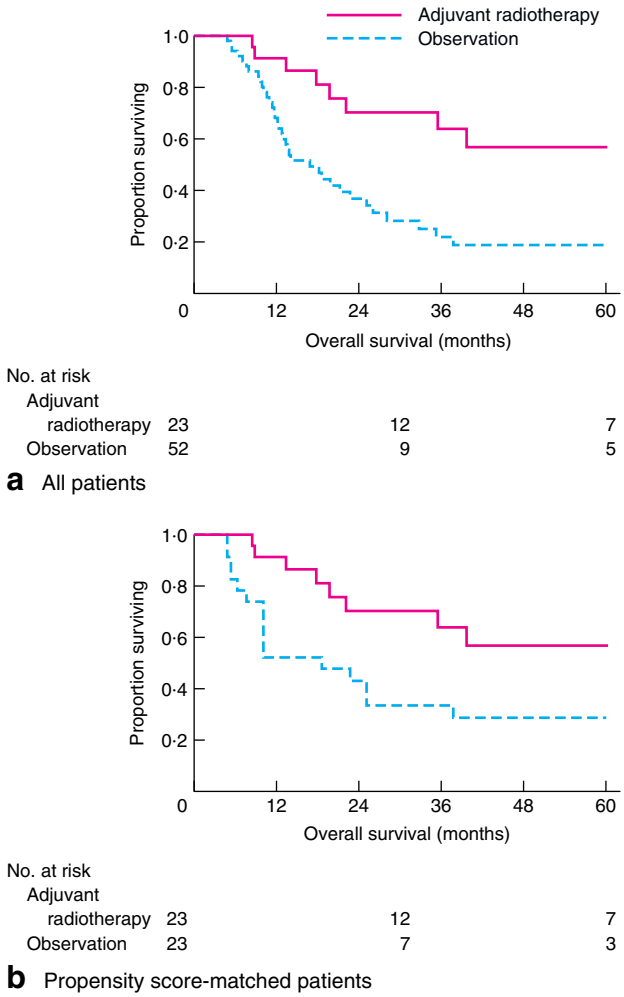

Fig. 3 Kaplan–Meier survival curves for **a** unselected patients and **b** propensity score-matched patients with a circumferential resection margin smaller than 1 mm treated by adjuvant radiotherapy or observation

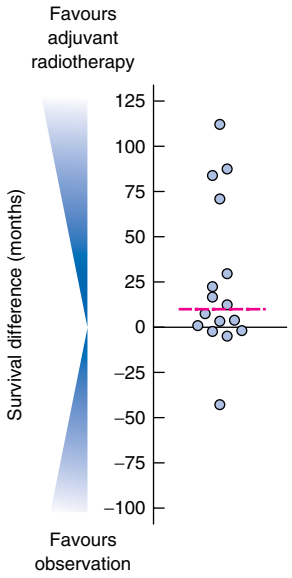

Fig. 4 Scatter plot of survival differences between propensity score-matched patients with a circumferential resection margin smaller than 1 mm treated by adjuvant radiotherapy or observation only. Data from informative pairs are presented ($n = 16$). Dashed red line represents the median difference. $P = 0{\cdot}021$ (Wilcoxon matched-pairs signed rank test)

Among propensity score-matched pairs, the estimated survival benefit for adjuvant radiotherapy was calculated as a median of 10 (range −43 to 112) months (*Fig. 4*).

Discussion

This study of pT3 oesophageal and OGJ cancers showed that a positive CRM of 1 mm or less was the optimal cut-off to identify patients with a poorer survival, and therefore supports the RCP classification. This is in agreement with seven previous studies that demonstrated a CRM of less than 1 mm to be independently predictive of prognosis[9–13,15,28]. In contrast, two studies have reported only a directly involved CRM to be independently predictive of prognosis[14,16]. One of these studies involved 132 patients with pT3 oesophageal adenocarcinoma undergoing surgery alone, and compared RCP and CAP classifications[16]. Only a positive CRM of 0 mm and histological vascular invasion were independently predictive of survival, although only 43 patients had a positive CRM of 1 mm or more so the study may have been underpowered to detect a survival difference between groups. The study was also unusual in failing to demonstrate an association between node status and survival. The second study examined 135 pT3 oesophageal cancers, but again only 52 patients had a positive CRM of 1 mm or greater and lack of power may have limited the conclusions drawn[14].

In the present study, the rate of CRM involvement and lymph node harvest were comparable with those in other series of resected pT3 cancers. Like others, a significant imbalance in known prognostic variables was found between groups stratified by the shortest distance from the tumour to the CRM[15,29]. Previous studies have attempted to control for the discrepancies in node status or tumour differentiation by considering only node-positive or -negative patients, or subdividing tumours by differentiation[10–12]. Although this approach can correct for one or two confounders, it is at the expense of diminishing discriminatory power. Multivariable analysis can correct for confounders, and Cox regression incorporating known prognostic variables established CRM group as independently predictive of prognosis in the present analysis.

PSMA permitted assessment of the contribution of the CRM to survival by correcting for known prognostic variables. This revealed equivalent survival in patients with a positive CRM of 0 mm and those with a CRM of 0·1–0·9 mm when the effect of known confounders was eliminated. Both groups had a significantly poorer survival than matched patients with a positive of CRM 1 mm or more, indicating that the RCP rather than the CAP definition of an involved CRM is more appropriate.

PSMA has been used in one other study to assess the effect of the CRM on survival after resection of oesophageal cancer[30]. Although the authors found no survival difference between matched groups, all of the patients underwent chemoradiotherapy followed by surgery and the patient numbers were small (44 for CRM less than 1 mm *versus* 1 mm or more; 8 for CRM 0 mm *versus* CRM more than 0 mm).

Differences in preoperative treatment limit comparisons between studies. Neoadjuvant chemoradiotherapy has been associated with a lower R1 rate than neoadjuvant chemotherapy[31,32]. A systematic review of trials of neoadjuvant chemoradiotherapy followed by surgery supports these findings, with a 15 per cent average rate of positive CRM less than 1 mm[33]. In the present study, among patients with a positive margin after neoadjuvant chemotherapy and surgery, there was a significant survival benefit of 10 months and a twofold relative reduction in the risk of death for those treated with adjuvant radiotherapy compared with observation alone. This benefit was apparent after correction for selection bias by propensity score matching for known prognostic variables. The idea that there may be a survival benefit with radiotherapy in the context of microscopic residual disease seems appealing.

The study does have limitations. In common with all observational studies, there was bias through patient selection. The management of patients with oesophageal cancer also changed during the study period, with the introduction of neoadjuvant chemotherapy leading to tumour downstaging in some patients. In an effort to minimize this effect, only patients with clinical T3 tumours before treatment were included. The present study also reported overall rather than disease-specific survival. This seems appropriate, as the majority of deaths after oesophagectomy for cancer are the result of this disease. Furthermore, the actual cause of death is often unclear without post-mortem examination, and death is often attributed to oesophagogastric cancer regardless of other possible conditions[34]. It is possible that the observed survival benefit following adjuvant radiotherapy resulted from selection bias in favour of patients who were physiologically more robust and able to withstand a month of radiotherapy shortly after major surgery. This bias was not corrected for by the matching analysis. For this reason, although the results are encouraging, they merit independent confirmation.

Acknowledgements

The authors thank G. Murray for statistical advice and other members of the South-East Scotland oesophagogastric multidisciplinary team for their support in this study, including L. Graham, M. Gibson, N. Bell, D. Ulic, C. Deans, G. Couper, P. Lamb, A. Paisley, A. De Beaux, I. Penman, J. Plevris, L. Wall, D. Patel, J. Anderson, K. Robertson and B. Langdale-Brown.

J.R.O'N. receives funding from the Wellcome Trust (grant no. 094417/Z/10/Z).

Disclosure: The authors declare no conflict of interest.

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